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Arthur M. Krieg, Iain Sim

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Coley Pharmaceutical Group, Inc.
93 Worcester St.
Suite 101
Wellesley, MA 02481 -

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Report Title

Final Report on ACCELERATE ANTHRAX: CpG 7909 Vaccine Adjuvant Program

ABSTRACT

A clinical study “Phase 1/2, Proof-of-Concept, Double-Blind, Randomized, Controlled Trial Assessing the Immunogenicity and Safety of Anthrax Vaccine Adsorbed (BioThrax?) Combined with CPG 7909 in Normal Volunteers” was completed and presented at the 2005 Interscience Conference on Antimicrobial Agents and Chemotherapy in a poster entitled “Marked Enhancement Of Antibody Response To Anthrax Vaccine Adsorbed With CPG 7909 In Healthy Volunteers“. The conclusions from this study included:

1. AVA plus CPG 7909 was reasonably well tolerated
2. There was a trend to greater frequency and severity of adverse events in the AVA plus CPG 7909 group compared to the AVA alone and CPG 7909 alone groups but this was not statistically significant
3. AVA plus CPG 7909 elicited a heightened (6 to 8-fold increase) and accelerated (21 to 24 days) antibody response ($p < 0.001$) compared to AVA alone
4. AVA plus CPG 7909 elicited a positive anti-PA antibody response in >50% of subjects within 14 days of a single immunization

A robust, large scale manufacturing process of CPG 7909 has been developed and is judged suitable for the supply of drug for further clinical studies and product commercialization.

List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Number of Papers published in peer-reviewed journals: 0.00

(b) Papers published in non-peer-reviewed journals or in conference proceedings (N/A for none)

Number of Papers published in non peer-reviewed journals: 0.00

(c) Papers presented at meetings, but not published in conference proceedings (N/A for none)

MARKED ENHANCEMENT OF ANTIBODY RESPONSE TO ANTHRAX VACCINE ADSORBED WITH CPG 7909 IN HEALTHY VOLUNTEERS

D. RYNKIEWICZ1, M. RATHKOPF2, J. RANSOM3, I. SIM4, L.GIRI5, J. QUINN2,T. WAYTES5, M. AL-ADHAMI4, W. JOHNSON6, C. NIELSEN7□1V.A. & U. of Texas Health Science Center, San Antonio, TX; 2Wilford Hall Medical Ctr,San Antonio, TX; 3Fast Track Drugs & Biologics, Potomac, MD; □4Coley Pharmaceutical Group, Wellesley, MA; 5Emergent BioSolutions, Gaithersburg, MD; □6USAMRIID, Ft. Detrick, MD; 7Consultant to DARPA, Arlington, VA

Number of Papers not Published: 1.00

(d) Manuscripts

Number of Manuscripts: 0.00

Number of Inventions:

Graduate Students

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Faculty Supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Total Number:

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

MARKED ENHANCEMENT OF ANTIBODY RESPONSE TO ANTHRAX VACCINE ADSORBED WITH CPG 7909 IN HEALTHY VOLUNTEERS

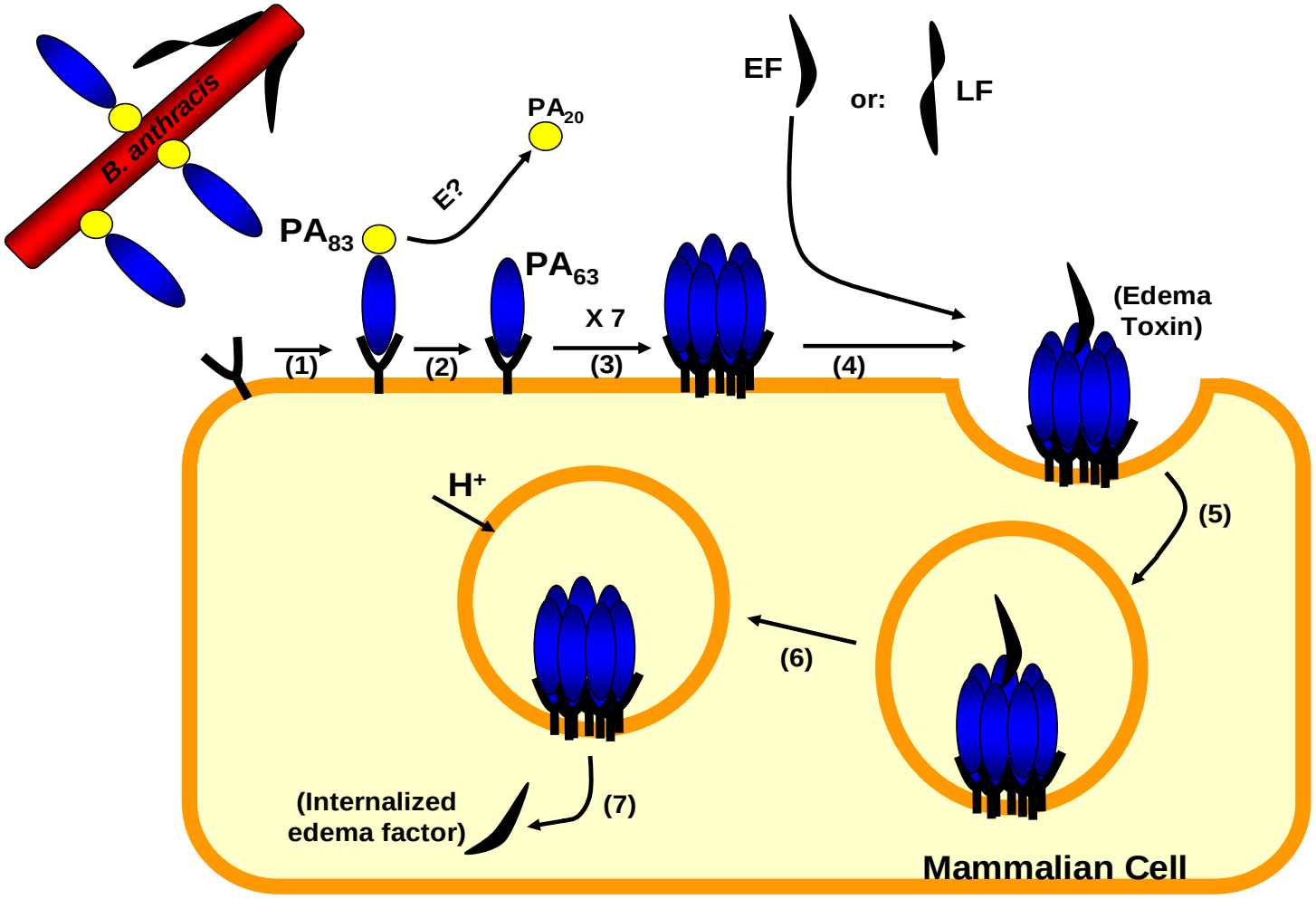
D. RYNKIEWICZ[1], M. RATHKOPF[2], J. RANSOM[3], I. SIM[4], L.GIRI[5], J. QUINN[2],T. WAYTES[5], M. AL-ADHAMI[4], W. JOHNSON[6], C. NIELSEN[7]

[1]V.A. & U. of Texas Health Science Center, San Antonio, TX; [2]Wilford Hall Medical Ctr,San Antonio, TX; [3]Fast Track Drugs & Biologics, Potomac, MD;

[4]Coley Pharmaceutical Group, Wellesley, MA; [5]Emergent BioSolutions, Gaithersburg, MD;

[6]USAMRIID, Ft. Detrick, MD; [7]Consultant to DARPA, Arlington, VA

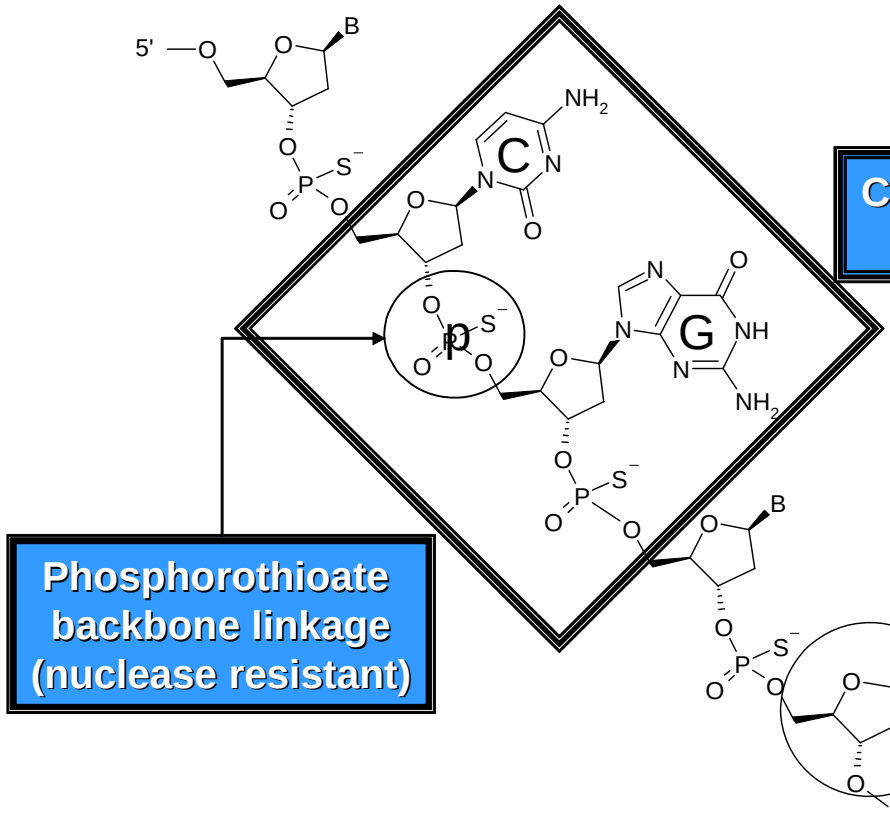
ROLE OF PA IN ANTHRAX PATHOGENESIS



Modified from: Miller, C.J.,Elliott, J.L. and Collier, J.L. Biochem 38: 10432 (1999)

CPG 7909 (VAXIMMUNE)

5′ – TCGTCGTTTTGTCGTTTTGTCGTT – 3′

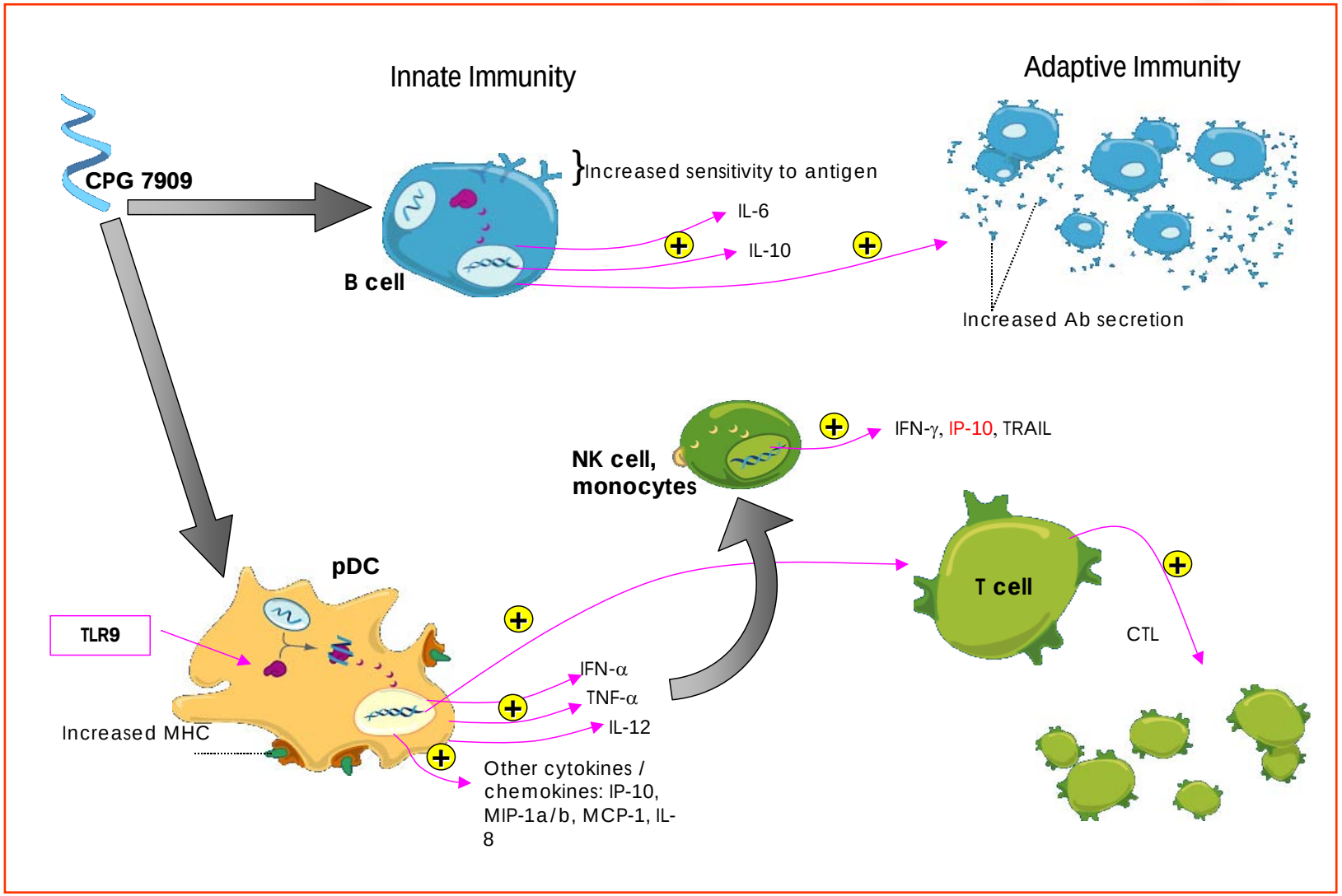


CpG motif activates TLR9 receptor

Phosphorothioate backbone linkage (nuclease resistant)

Sugar (deoxyribose)

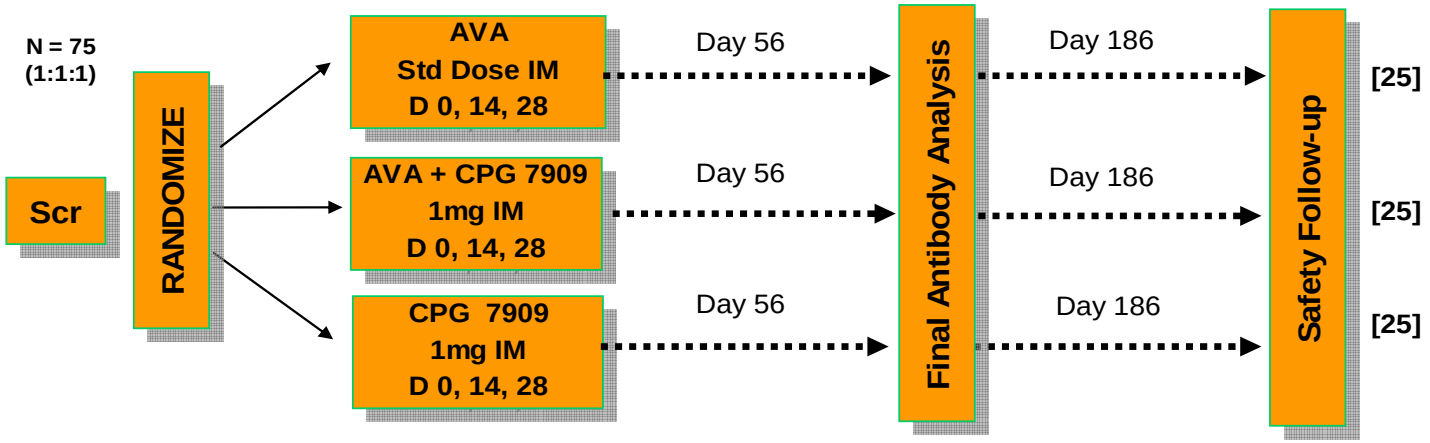
MECHANISM OF ACTION OF CPG 7909



CLINICAL STUDY DESIGN

ANTHRAX VACCINE ADSORBED PLUS CPG 7909 CLINICAL STUDY DESIGN

Phase I/II proof-of-concept, double blind, randomized, controlled trial in healthy volunteers



- Healthy volunteers, age 18-45 years, male and female, at 2 study sites
- Subjects received study treatment on days 0, 14 and 28
- Subjects assessed for anti-PA and anti-TNA antibody response on days 7, 10, 14, 16, 21, 24, 28, 30, 35, 42, 49, 56.
- Safety assessed before immunization and at least weekly in clinic through day 56 and at month 6, reviewed subject-maintained diaries

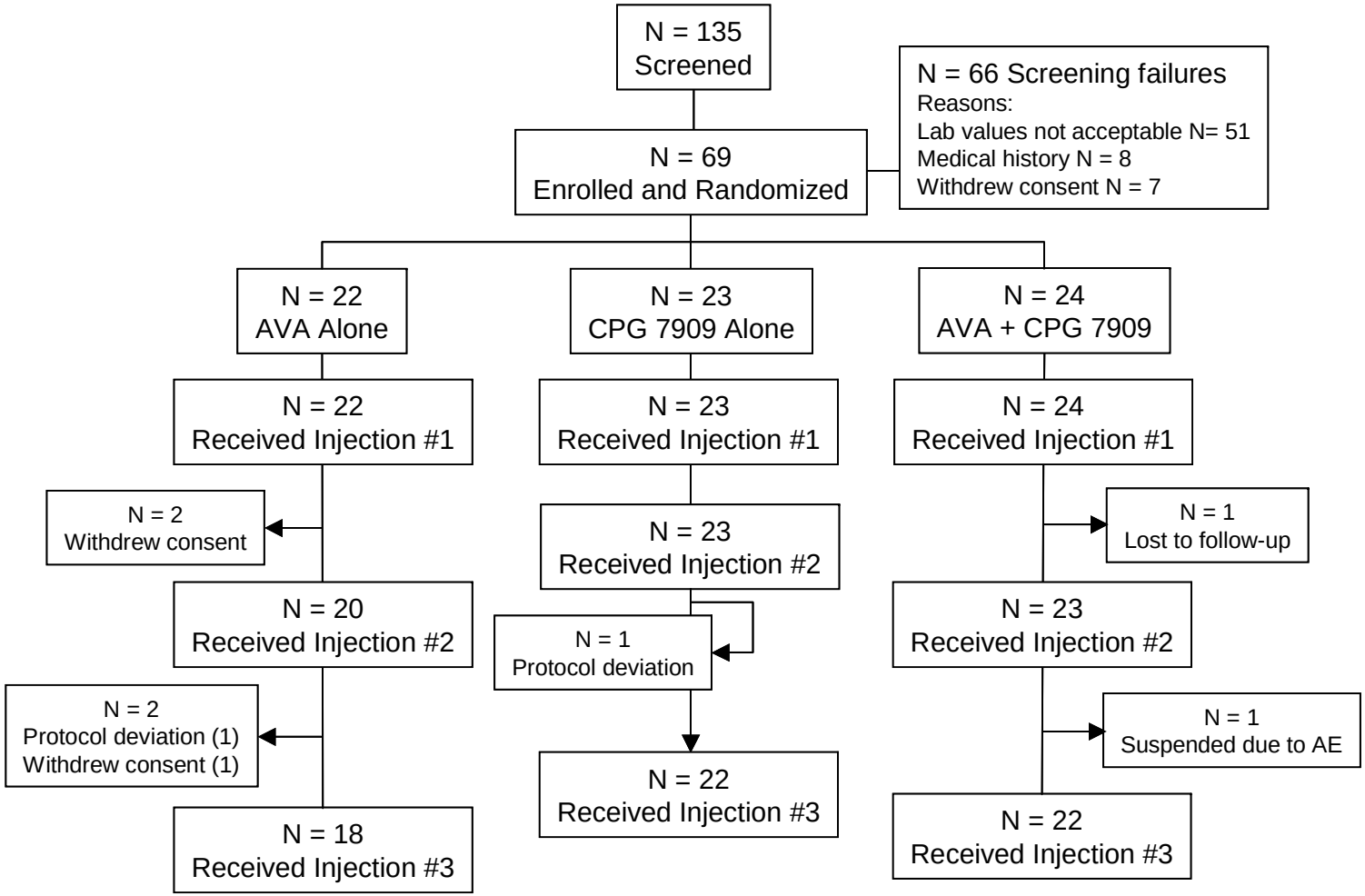
DEMOGRAPHICS

Demographic Characteristics of All Randomized Subjects

Characteristic	AVA alone	CPG 7909 alone	AVA + CPG 7909	All 3 Groups
Gender – n	22	23	24	69
Male, n (%)	11 (50.0)	12 (52.2)	12 (50.0)	34 (49.3)
Age (at consent) – n	22	23	24	69
Mean (SD)	25.8 (5.8)	27.5 (4.7)	29.0 (6.7)	27.5 (5.9)
Median	24.0	26.0	27.5	26.0
Race – n (%)	22	23	24	69
White	18 (81.8)	18 (78.3)	18 (75.0)	54 (78.3)
Black/African Amer.	0 (0)	0 (0)	1 (4.2)	1 (1.5)
Asian	1 (4.6)	1 (4.4)	4 (16.7)	6 (8.7)
Not specified	0 (0)	1 (4.4)	0 (0)	1 (1.5)
Others[a]	3 (13.6)	3 (13.0)	1 (4.1)	7 (10.1)
Ethnicity – n (%)	22	23	24	69
Non-Hispanic	17 (77.3)	15 (65.2)	21 (87.5)	53 (76.8)
Hispanic or Latino	5 (22.7)	8 (34.8)	3 (34.8)	16 (23.2)

[a]Others include those who reported a race that was not listed on the demographics case report form or who reported multiple races. Races not represented were excluded from the table listing.

DISPOSITION OF TRIAL SUBJECTS



SUMMARY OF EFFICACY

Mean peak antibody concentration was 6.3-fold (anti-PA) and 8.8-fold (TNA) greater in the AVA plus CPG 7909 group, both p<0.001

The maximum anti-PA concentration (220µg/mL) achieved in the AVA group (median time 42.5 days) was achieved 21 days earlier in the AVA plus CPG 7909 group (p<0.001)

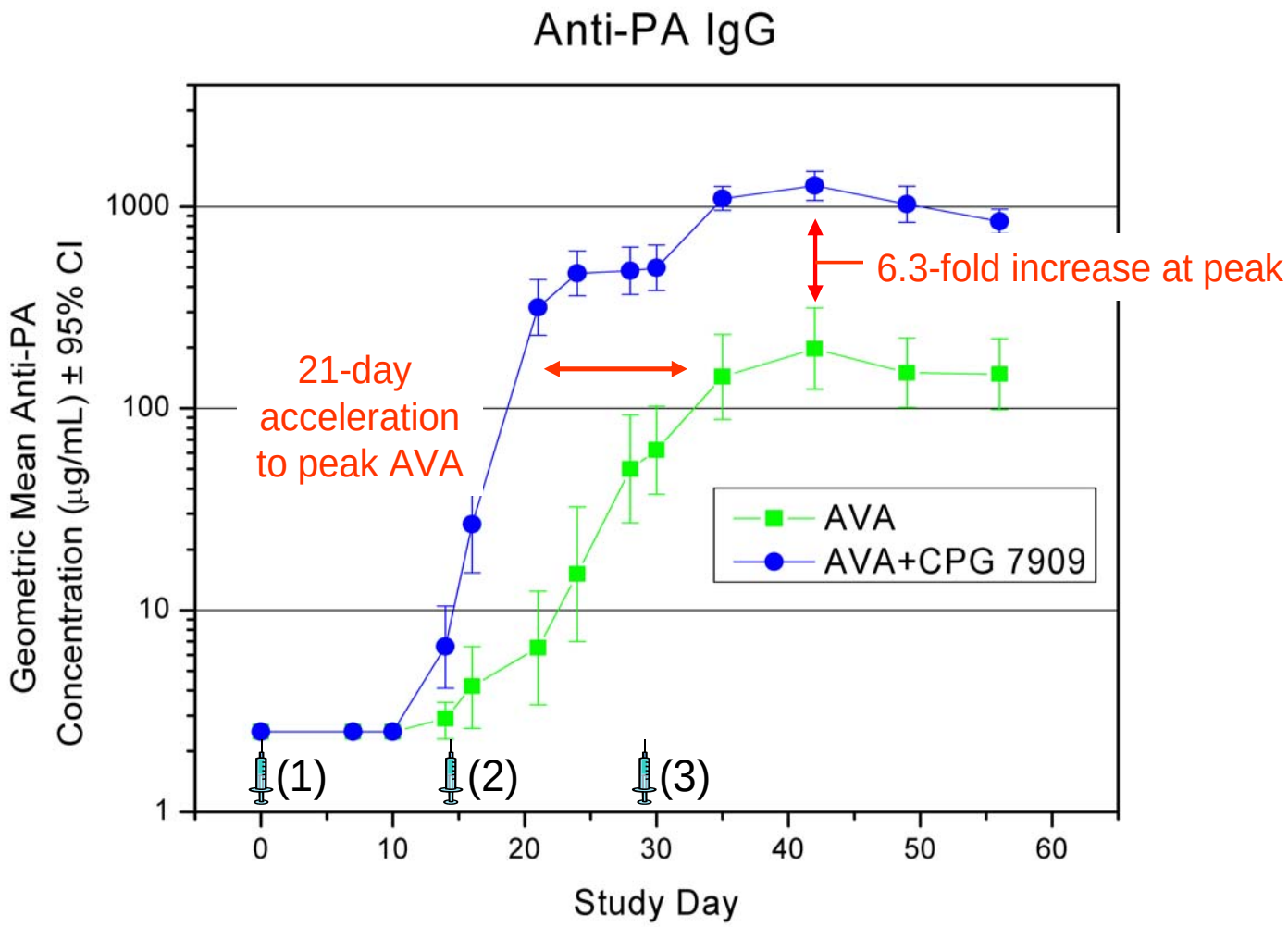
The maximum TNA concentration (159µg/mL) achieved in the AVA group (median time 46 days) was achieved 24 days earlier in the AVA plus CPG 7909 group (p<0.001)

12 of 22 (55%) of subjects in the AVA plus CPG 7909 group were seropositive for anti-PA after a single immunization (day 14) compared to 2 of 18 (11%) of subjects in the AVA alone group

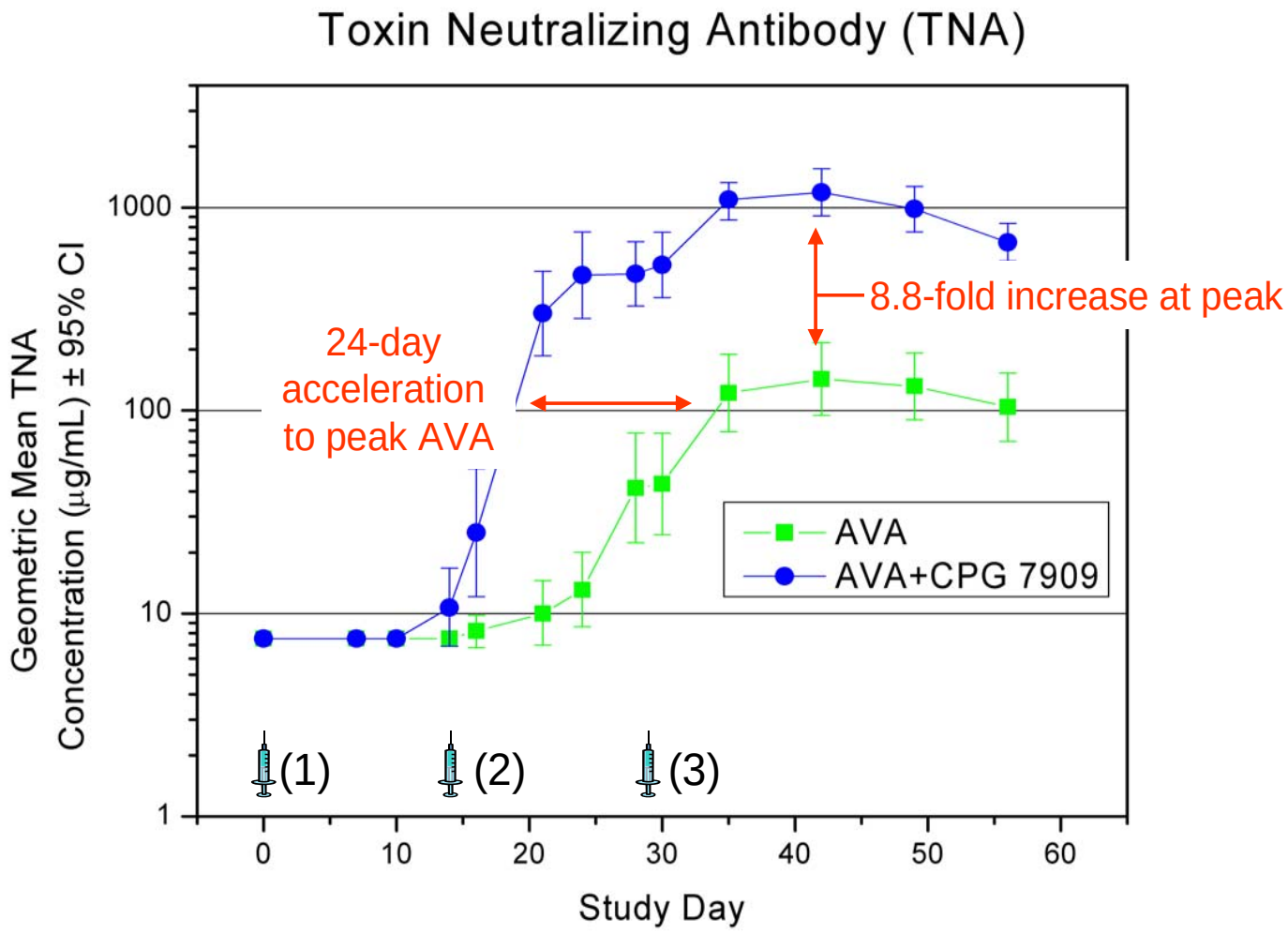
Significant difference in the geometric mean anti-PA antibody concentrations between the AVA and AVA plus CPG 7909 arms first detected at Day 14 (p<0.001)

At peak response, 22/22 (100%) subjects in the AVA plus CPG 7909 group achieve an anti-PA concentration of ≥ 220µg/mL compared to only 11/18 (61%) of subjects in the AVA alone group

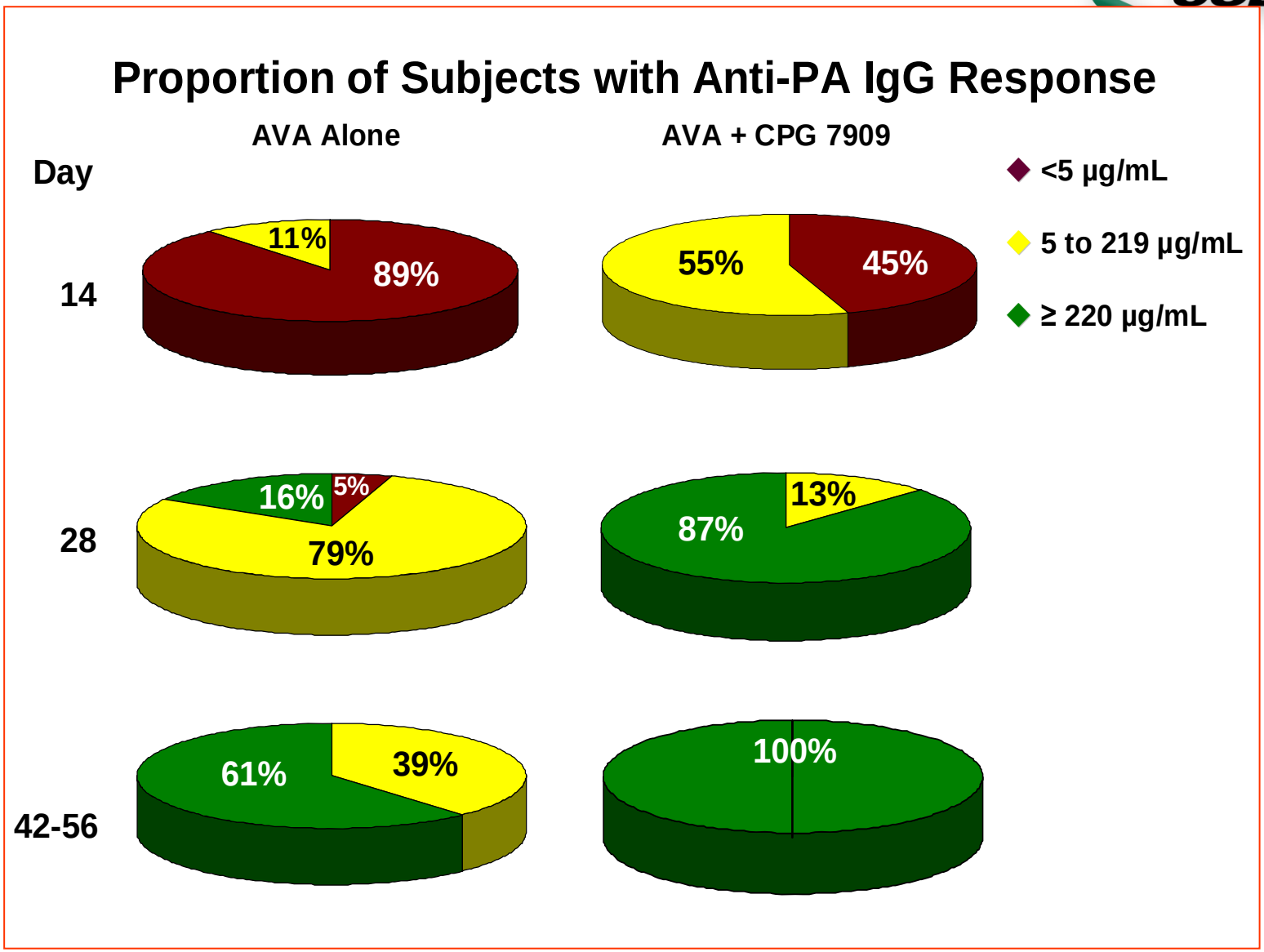
RESPONSE TO ANTRAX PA (ELISA)



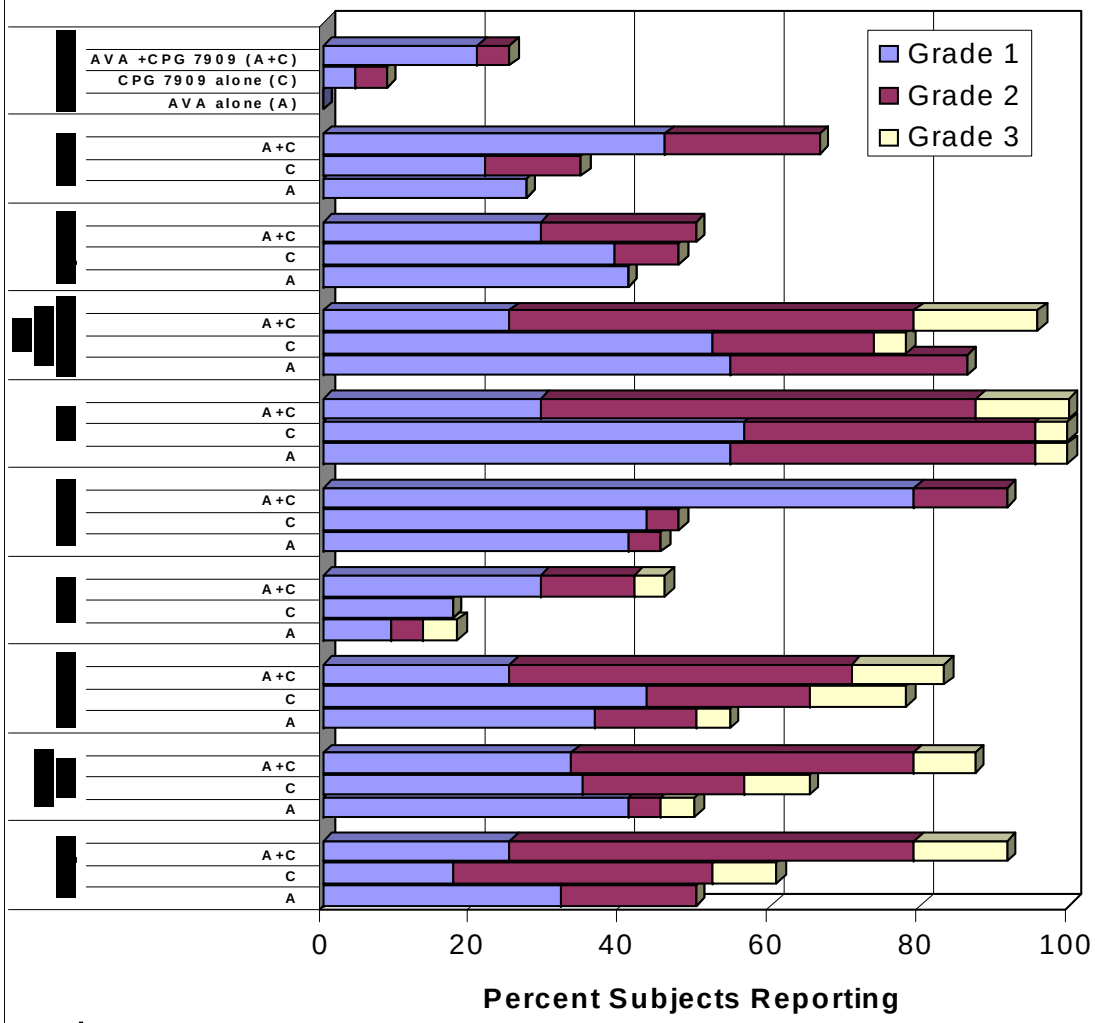
TNA RESPONSE



RATE OF SEROCONVERSION



SAFETY



*Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials – FDA, April 2005

LABORATORY FINDINGS

- **No clinically significant changes in laboratory analyte levels were observed.**
- **Grade one leukopenia was seen in all study arms.**
- **Hypokalemia was reported in 50%, 43.5%, and 62.5 % of participants in the AVA, CPG 7909, and AVA + CPG 7909 groups, respectively, suggesting that potassium levels may have been affected by the combination treatment.**

CONCLUSIONS

Safety

AVA plus CPG 7909 was reasonably well tolerated

The local injection site reactions and systemic symptoms were expected and were the most common adverse events

There was a trend to greater frequency and severity of adverse events in the AVA plus CPG 7909 group compared to the AVA alone and CPG 7909 alone groups but this was not statistically significant

Immunogenicity

AVA plus CPG 7909 elicited a heightened (6 to 8-fold increase) and accelerated (21 to 24 days) antibody response ($p < 0.001$) compared to AVA alone

AVA plus CPG 7909 elicited a positive anti-PA antibody response in >50% of subjects within 14 days of a single immunization